REMARKS

Status Summary

Claims 1-31 are pending. Claims 1-6 and 10-31 are withdrawn from consideration as directed to a non-elected invention, and claims 7-9 were examined. Claims 7-9 are rejected under 35 U.S.C. § 112, first paragraph. Claim 7 is amended herein. New claims 32-37 are added. Reconsideration in view of the amendments and following remarks is respectfully requested.

Objection to the Specification

The specification is objected for incorrect presentation of trademarks (*i.e.*, non-capitalization). Official action, page 2, item 1. The specification is amended as indicated above to capitalize trade names, including the anti-CD20 antibody RITUXAN® (rituximab). Applicant also clarifies that the term "rituximab" is a common name used to describe a chimeric anti-CD20 antibody useful in the claimed methods. In support thereof, a letter from the United States Adopted Names Council, which formally recognizes the common use name "rituximab" is enclosed herewith.

Objections to the Claims

Claim 7 is objected to for use of the language "appreciable" to describe tumor regression. Official action, page 2. The claim is amended to refer to subjects who fail to show appreciable tumor remission or regression as "refractory," which is conventional terminology used in the art and throughout the instant application as originally filed. Based thereon, the objection to claim 7 is believed to be moot.

First Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

Claims 7-9 are rejected under 35 U.S.C. § 112, first paragraph as allegedly not enabling one skilled in the art to practice the invention. In particular, the examiner states that the specification lacks data demonstrating that treatment of a subject having B cell lymphoma, which subject has not exhibited appreciable tumor regression in response to administration of a chimeric anti-CD20 antibody, via administration of a radiolabeled anti-CD20 antibody, as now claimed. In the view of the examiner, down regulation of tumor antigen is known, and thus one cannot predict whether repeat dosing using antibodies that recognize a same antigen

can be effective. The examiner also contends that cancer treatment in general is unpredictable. Official action, pages 3-7. This rejection is respectfully traversed.

The legal standard for enablement is whether one reasonably skilled in the art could make and use the invention based on the disclosure of the application and knowledge in the art without undue experimentation. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). Compliance with the enablement requirement does not require actual reduction to practice prior to filing if the application fully discloses how to practice the invention. *Gould v. Quigg*, 822, F.2d 1074, 3 USPQ2d 1302 (Fed. Cir. 1987). *See also* MPEP § 2164.02. Evidence may be submitted after the filing date to demonstrate that the claimed invention works. MPEP § 2164.05.

The specification as originally filed discloses methods for treatment of B cell lymphoma in subjects that have relapsed or are refractory to other treatment(s), including prior treatment with a non-radiolabeled chimeric anti-CD20 antibody. *See e.g.*, page 3, lines 15-22, wherein it is described that patients having minimal or no response to treatment with a non-radiolabeled anti-CD20 antibody can positively respond to administration of a radiolabeled anti-CD20 antibody. Methods for administering a radiolabeled anti-CD20 antibody are disclosed in the specification, including, for example, at page 3, line 23, through page 4, line 2, wherein it is described that a radiolabeled anti-CD20 antibody can be administered from about one week to about two years following prior anti-CD20 therapy; and at page 34, lines 2-3, wherein it is described that a radiolabeled anti-CD20 antibody can be administered at dosages of 0.2, 0.3, or 0.5 mCi/kg; among other places.

Using the methods disclosed in the application as originally filed, administration of radiolabeled anti-CD20 antibody shows therapeutic efficacy in patients that are unresponsive to unlabeled anti-CD20 therapy. *See* Witzig et al. (2002) *J Clin Oncol* 20(15):3262-69 (copy enclosed). This study evaluated ibritumomab tiuxetan, a radiolabeled anti-CD20 antibody, for treatment of rituximab-refractory follicular non-Hodgkin's lymphoma. Patients identified as unresponsive to rituximab therapy received an initial pretreatment with rituximab at 250 mg/m^2 (iv) on days 1 and 8, followed by administration of ^{90}Y-labeled anti-CD20 (ibritumomab tiuxetan) at a dosage of 0.4 mCi/kg (iv) on day 8. The dosages and administration regimens used are described in the instant application, as noted above. The overall response rate for 54 patients with follicular NHL was 74% (15% complete responses and 59% partial responses), demonstrating that performance of the claimed methods has therapeutic efficacy in patients with refractory and relapsed B cell lymphoma.

Based on the foregoing arguments, claim 7 is believed to fully comply with the enablement requirement of 35 U.S.C. § 112, first paragraph. Original claims 8-9 and new claims 32-37 ultimately depend from claim 7 and are also believed to fully enable practice of the invention. Thus, the applicant respectfully requests that this rejection under § 112, first paragraph, be withdrawn.

Second Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

Claims 7-9 are further rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to enable methods for treating any B cell lymphoma. In the view of the examiner, the specification only enables treatment of non-Hodgkin's lymphoma. In particular, the examiner points to page 34 of the specification, where it is described that patients having mantle cell disease were unresponsive to radiolabeled rituximab therapy. Official action, pages 7-8. This rejection is also traversed.

The amount of guidance needed to enable an invention is inversely related to the amount of knowledge in the art and the predictability of the art. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970). *See also* MPEP § 2164.03. For a claimed genus, representative examples together with a statement applicable to the genus, is ordinarily sufficient to meet the enablement requirement. MPEP § 2164.02.

As described further below, the application includes representative examples of treatment methods for a substantial number of B cell lymphomas. Based on the reported success of when using these methods (*e.g.*, see Table I at pages 14-15), it is clear that the level of skill in the art and predictability of anti-CD20 therapy are high. Thus, the specification fully enables treatment methods for the genus of B cell lymphomas.

The specification as originally filed states that the disclosed therapeutic methods are useful for the treatment of various B cell lymphomas, including low grade, intermediate grade, and high grade non-Hodgkin's lymphomas, which are alternately described as indolent or aggressive lymphomas. *See e.g.*, page 6, line 15, through page 7, line 21. Also disclosed are working examples of treatment regimens for representative indolent B cell lymphomas, including low grade or follicular non-Hodgkin's lymphoma (page 13, line 10, through page 18, line 27), Waldenstrom's macroglobulinemia (page 19, lines 1-13), and chronic lymphocytic leukemia (page 19, line 14, through page 20, line 12). Additional working examples describe the treatment of aggressive lymphomas, such as intermediate grade and

high grade non-Hodgkin's lymphomas, including diffuse large cell lymphoma and mantle cell lymphoma (page 29, lines 19-27).

The clinical study of Witzig et al. employed methods of the instant disclosure for the treatment of patients having non-Hodgkin's lymphoma, small lymphocytic NHL, and transformed diffuse large-cell NHL (*see* page 3264, column 1). As described by Witzig, radiolabeled anti-CD20 antibodies are effective for the treatment of subjects having these various B cell lymphomas, and who are refractory to therapy with a non-radiolabeled anti-CD20 antibody.

It has also been observed that radiolabeled anti-CD20 antibodies elicit a more robust therapeutic response when compared to non-radiolabeled anti-CD20 antibodies, which correlation is independent of the extent of disease. *See* Witzig et al. abstract in Petryk & Grossbard (2001) *The Oncologist* 6:317-26. Thus, radiolabeled anti-CD20 antibodies of the invention are reasonably expected to be therapeutic in subjects that are responsive to rituximab treatment, which includes low-grade lymphomas as well as intermediate-grade and high-grade lymphomas. *See* Anderson et al. (1997) *Biochem Soc Trans* 25:705-8; Colombat et al. (2001) *Blood* 97:101-6; Coiffier et al. (1998) *Blood* 92:1927-32; Endo (1999) *Gan To Kagaku Ryoho* 26:744-8; Foran et al. (2000) *J Clin Oncol* 18:317-24; Hainsworth et al. (2000) *Blood* 95:3052-6; Maloney et al. (1997) *Blood* 90:2188-95; McLaughlin et al. (1998) *J Clin Oncol* 16:2825-33; Piro et al. (1999) *Ann Oncol* 10:655-61; Byrd et al. (2001) *J Clin Oncol* 19(8):2153-2164; Davis et al. (1999) *J Clin Oncol* 17(6):1851-1857 (copies enclosed) Following a review of the instant application, which includes working examples for treatment of these various lymphomas, a skilled artisan could perform the claimed invention in the absence of undue experimentation.

With regard to mantle cell lymphoma, the examiner points to clinical results wherein three patients having mantle cell are described as non-responsive to treatment with radiolabeled anti-CD20 antibody (pages 33-34 of the specification). Given the limited sample size of patients having mantle cell lymphoma, it is premature to conclude that radiolabeled anti-CD20 antibodies are ineffective for treatment. As noted above, it is expected that radiolabeled anti-CD20 antibodies are useful for the treatment of mantle cell lymphoma based on the therapeutic efficacy of non-radiolabeled anti-CD20 antibodies for mantle cell treatment (Coiffier et al. (1998) *Blood* 92:1927-32; Foran et al. (1999) *Ann Oncol* 10:33) and the observed superior performance of radiolabeled versus non-radiolabeled anti-CD20 antibodies (Witzig et al. abstract in Petryk & Grossbard (2001) *The Oncologist* 6:317-26).

Based on the foregoing, the specification is believed to fully enable the scope of original claims 7-9 and new claims 32-37 as directed to radiolabeled anti-CD20 therapy of B cell lymphomas. Thus, the applicant respectfully requests that this rejection under § 112, first paragraph, be withdrawn.

Discussion of New Claims

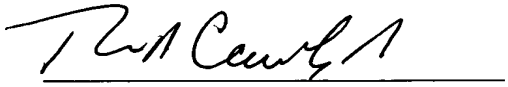
New claims 32-37 are added to claim particular aspects of the invention. The new claims read on the previously elected species of intermediate grade lymphoma. No new matter is introduced. Support for the new claims can be found in the application as originally filed, including at page 34, lines 7-10, wherein clinical studies in rituximab-refractory patients is described; at page 10, lines 20-23, wherein the therapeutic use of 90Y-labeled antibodies is described; at page 11, lines 23-24, wherein ^{131}I-labeled antibodies are described; at page 33, lines 19-25, wherein treatment methods are described comprising administration of a non-radiolabeled chimeric anti-CD20 antibody (rituximab) followed by administration of a non-radiolabeled anti-CD20 antibody (^{90}Y-labeled murine anti-CD20 antibody 2B8).

Conclusion

All objections and rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If any points remain in issue, which the examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

PILLSBURY WINTHROP LLP



Thomas A. Cawley, Jr., Ph.D.
Registration No. 40,944

P.O. Box 10500
McLean, VA 22102
(703) 905-2144 Direct Dial
(703) 905-2500 Facsimile

November 25, 2003

TAC/JBM